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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,842	07/05/2000	KAZUYUKI SUGIYAMA	Q60017	2682

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EXAMINER

DO, PENSEE T

ART UNIT	PAPER NUMBER
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1641

DATE MAILED: 02/11/2003

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/582,842

Applicant(s)

SUGIYAMA ET AL.

Examiner

Pensee T. Do

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 November 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,6-12 and 24-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,6-12 and 24-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1. 6) ☐ Other: _____

DETAILED ACTION

Amendment Entry

The amendment filed on November 4, 2002 has been acknowledged and entered.

Claims 1-3, 6-12, 24-30 are pending.

Specification

The abstract of the disclosure is objected to because the priority information is not disclosed in the first line of page one. Correction is required. See MPEP § 608.01(b).

Withdrawn Objections & Rejections

Rejections under 35 USC 112, 2nd paragraph regarding the objection to the term "capable of" and USC 112, 1st paragraph are withdrawn herein.

Response to Arguments

Applicant's arguments filed November 4, 2002 have been fully considered but they are not persuasive.

Regarding the 112, 2nd paragraph rejection about "crosslinked-avidin", applicants argue that there is a clear discussion of the meaning of the term "crosslinked avidin" in the specification at page 7, lines 3-23. Therein, it is explained that crosslinked avidin is a protein in which there exist crosslinkages at least between subunits, i.e. intramolecular crosslinkages.

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26

USPQ2d 1057 (Fed. Cir. 1993). The term "crosslinked avidin" can have another meaning, other than "intramolecular linkages", such as that the avidin is bound to a linker which links the avidin and biotin together.

Regarding the rejection under USC 103(a) by Haughland in view of Giese, Applicants respond that Geise discloses "cross-linked avidin" as a typical example of avidin derivatives. There is no further discussion of crosslinked avidin or its properties. There is no support for the examiner's position that crosslinked avidin is more stable and leads to a higher-affinity binding substance. The only disclosure of such preferred properties of crosslinked avidin is in Applicant's specification. Thus, the examiner is using improper hindsight to provide the motivation of using the crosslinked avidin of Giese in the biotin-avidin-biotin complex of Haughland.

Giese teaches that a multiple layer process and multiple layer product comprise a protein such as avidin and a ligand material such as biotin (and any derivatives, analogs or substitutes of these which still comprise analogous binding interaction) and a material referred to as an extender. (see col. 1, lines 59-69). Giese also teaches avidin derivatives as crosslinked avidin. (see col. 2, lines 9-11). Giese then teaches performing a derivatization reaction for example crosslinking or modifying of functional groups in between any of the steps of the multiple layer process comprising successive or repetitive attachment of the protein and extenders to a surface to build up alternate layers of each to change the properties further for example to provide a more complete coverage of the surface, more stability, different functional groups, etc. Thus, one of ordinary skills in the art would have found it obvious that the each layer comprising

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either biotin or avidin can be derivatized to produce a stable surface for attachment of molecules to be detected, for example when being used as a capture support in an immunoassay. As Giese teaches, when the surface of avidin is modified or derivatized (which avidin become crosslinked avidin) such avidin surface is more stable and thus would have a high affinity of attaching other molecules to such surface.

Regarding the 103 rejection by Haughland and Giese further in view of Tatsumi, Applicants argue that the Examiner's content that "the biotinylated firely luciferase of Tatsumi is more active and sensitive when compared to conventional chemically modified biotinylated firely luciferase that is not in the form of a fusion protein" is not a statement of motivation to combine the references and thus appears to be just the examiner's position.

The movitation to combine the reference is clear as it would have been obvious to one of ordinary skills in the art to use the fused protein of Tatsumi in the combined method of Haughland and Geise for detecting the activity of luciferase since Tatsumi teaches that the biotinylated firely luciferase in his invention yields a much higher percentage of activity upon binding to streptavidin compared to conventional chemically modified biotinylated firely luciferase that is not in the form of a fusion protein, and Haughland teaches an enzyme immunoassay method of using binding agen-biotin-avidin-biotin-enzyme to the advantage that the fusion protein (biotinylated firely luciferase) of Tatsumi is more active and sensitive when compared to conventional chemically modified bitionylated firely luciferase that is not in the form of a fusion protein.

Maintained Rejection(s)

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6-12, 24-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For claims 1, 2, 6-12, 24-30, "crosslinked avidin" is unclear because such term would be interpreted in many ways such as many avidins crosslinked together since biotin binds to the avidin naturally without the aid of a crosslinker or that the avidin is bound to a linker which links the avidin and the biotin together.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 6, 7-9, 12, 24, 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haughland et al. (US 5,443,986) further in view of Giese (US 4,478,914).

Haughland teaches a biotin-avidin-biotin complex comprising two biotin-introduced products which are the same or different (see table 12 in col. 22); and a avidin sandwiched therebetween (see col. 22, table 12) wherein at least one of the two

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biotin-introduced products is labeled and the other one is a biotin-introduced binding component (see col. 22). Haughland also teaches an enzyme-mediated technique such as enzyme-linked immunosorbent assay (ELISA) to detect analytes (see col. 22, lines 4-51). The method of the assay comprises combining the biotin-introduced enzyme, the sample containing analyte, and the biotin-binding component, an avidin to connect the two biotins together. The signal of the enzyme is detected. The binding component is a DNA (see col. 22, table 12). The biotin-introduced labeling substance is a biotin-introduced enzyme (see col. 22, table 12). Kits containing reagents for carrying out the methods are also disclosed in Haughland (see col. 40, example 19).

However, Haughland fails to teach a cross-linked avidin.

Giese teaches a process comprises of applying alternate successive layers of a first or second materials to a surface to be modified. The first material comprises a ligand binding proteinaceous material and the second material comprises a reactive ligand extender material, wherein the proteinaceous first material is selected from the group consisting of lectins, protein A, avidin derivatives including a crosslinked avidin, streptavidin, antibodies and combinations thereof, the second material is selected from biotin, biotin derivatives, biotin analogs, Fc fragments, hapten and combinations thereof. Avidin is a protein found in egg whites. (see col. 1, lines 15-20; line 50-col. 4, line 62).

It would have been obvious to one of ordinary skill in the art to use the crosslinked avidin of Giese in the method of Haughland since Giese's end product would have layers of biotin-avidin-biotin on a solid support. Furthermore, the crosslinked avidin is more stable and has high biotin affinity than the non-crosslinked avidin and

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thus the complex of biotin-crosslinked avidin-biotin would be more stable. An increase in affinity and stability between the avidin and the biotin would be an advantage in reduced product storage. Assays and kits comprising increased affinity avidin, because of the additional stability, have a longer shelf and less fastidious in shipping and storage requirements. The enhanced stability of these assays and kits would reduce the cost to the consumer. Regarding claim 8, since Giese teaches that the second material is a biotin or biotin derivatives, Fc fragments, and combinations thereof, it would have been obvious to one of ordinary skills in the art to combine biotin and Fc fragments to detect antigen since antibody fragment such as Fc fragment efficiently binds to the antigen more specifically with high affinity.

Claims 10, 11, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haughland et al. (US 5,443,986) and Giese further in view of Tatsumi (US 5,843,746).

Haughland et al. and Giese have been discussed above.

However, Haughland and Giese fail to teach a biotin-introduced fused-protein of an enzyme such as a biotin-introduced luciferase.

Tatsumi teaches a fusion protein (biotinated firely luciferase) which can be applied to a variety of bioluminescent analysis methods. For example, the biotinated firely luciferase can be bound through the biotin thereof to avidin or streptavidin to form a luciferase complex and a luminescent analysis method using such a firely luciferase complex can be applied to a detection system using biotin-avidin in techniques such as enzyme immunoassays, DNA probe method, immunostaining, receptor measurement,

in situ hybridization, etc. (see col. 3, lines 33-41; col. 4, lines 25-35). Tatsumi also teaches using goat anti-mouse IgG Fc fragment-specific polyclonal antibody in the method of detecting for the enzyme activity. (see col. 7, lines 40-55).

It would have been obvious to one of ordinary skill in the art to use the fused protein of Tatsumi in the combined method of Haughland and Giese for detecting the activity of luciferase since Haughland teaches an enzyme immunoassay method of using binding agent-biotin-avidin-biotin-enzyme and the enzyme luciferase of Tatsumi can be biotinylated. Since the biotinated firely luciferase of Tatsumi yields a much higher percentage of activity upon binding to streptavidin compared to that of a chemically modified biotinated firely luciferase, e.g. 93% to 62% respectively. Furthermore, the biotinated firely luciferase of Tatsumi attains 10 times sensitivity as high as the conventional chemically modified biotinated firely luciferase. With respect to the fragment Fab', since it depends on the analyte being detected, one of ordinary skill in the art would find it obvious to use fragment Fab's in the detection of antigen since fragment Fab' provides specificity

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the

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shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 703-308-4398. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 703-305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-746-5291 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Pensee T. Do
Patent Examiner
February 6, 2003


CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP 1800-1641
2/6/03